A. Terminal Disclaimers

Applicants, in response to the obvious-type double patenting issues raised by the examiner, include herewith terminal disclaimers disclaiming any term of any claims which may be granted in this case that would expire after the expiry date of any patents issued in related applications 09/958,050; 10,066,964; 10/066,836; and 10/067,020.

The filing of these terminal disclaimers has been made without prejudice solely to expedite prosecution. These disclaimers have no impact on patent term, as all cases mentioned will expire on the same date. Applicants, as a matter of record, rejects that such obvious-type double patenting is present. Applicants herein reserve all rights in distinguishing such issues should the need arise. The aqueous formulations claimed in this application are not believed to be obvious in light of the disclosure of a genus of compounds including the 17α-furan-2-yl compound of the instant formulation claims as in the 09/958,050 application; or the claims of the HFA solution formulations claimed in USSN 10/066,964; or the formulations of the 17α-furan-2-yl ester in combination with a long acting beta-agonist as claimed in 10/066,836; or the aqueous suspension formulations claimed in 10/067,020. Each instance involves particular issues to which applicant has found unique solutions to.

B. Prior Art Rejections:

1. Claims 4, 7, 10, 12, 13-15:

a. Claim 4

Claim 4 was rejected as obvious under 35 USC 103 over Sjoquist in light of Adjei. Sjoquist relates to an aqueous solution of corticoids including fluticasone propionate formulated as surfactant micellular structures. Adjei teaches specific liquified fluorocarbon propellant formulations containing suspended micellular drug particles in pressurized metered dose inhalers, the micelles being formed from surfactants.

In this Amendment, Claim 4 has been rewritten in dependent form incorporating those limitations from claims 1 and 2 from which it previously depended. As such, claim 4 requires 17α-furan-2-yl form of fluticasone. Although the

Adjei reference discloses in a laundry list of drugs and medicaments suitable for use in the described fluorocarbon ("FC") suspensions, including fluticasone, fluticasone, esters, including phosphate, monohydrate and furoate, the Adjei reference fails to disclose the 17α-furan-2-yl molecule per se as claimed as part of claim 4. Thus, each and every element of the claim is not found per se in the combined prior art references, as set forth in MPEP 2143.03.

Further, the manner in which the furoate ester class has been described in Adjei provides no probative support for activity. In particular, Adjei provides that a laundry list of generally known classes of drugs and medicaments that Adjei indicates can be formulated in their FC suspension formulation. This laundry list includes "fluticasone, fluticasone esters, including phosphate, monohydrate and furoate." No data is provided indicating any member contained within the phosphate or furoate ester classes has therapeutic activity, let alone how to make members of these classes, or what those classes represent in terms of actual members. As one of ordinary skill would be aware that fluticasone propionate is the only FDA approved commercially available ester of fluticasone, they would view this disclosure only a list of materials which might be possibly be manufacturable and if so, might possibly be active as medicaments. It is noteworthy that Adjei does not set forth a manner for making such ester classes, nor is any form of fluticasone ester actually exemplified. The speculative nature of Adjei's disclosure is more apparent as a "monohydrate" is not a class of ester. The mere possibility that such a class of speculative compounds might be made, might be formulated in the disclosed FC suspension MDI formulations and might have activity, it not the level of teaching of probability that would indicate to one of ordinary skill in the art that they could take this compound class from such a laundry list, select from this class the specific 17α-furan-2-yl compound as in claim 4, manufacture this non-disclosed compound without guidance on how such would be accomplished, and then reformulate this non-disclosed molecule in a completely different aqueous solution formulation, with the expectation that the resulting product would function successfully. At best this is a stretched "obvious to try" scenario, which clearly is not the appropriate manner for determining obviousness under the law. As such, a prima facie case of obviousness has not been established, and withdrawal of this rejection is therefore respectfully requested.

Even assuming a prima facie case of obviousness has been made out, the evidence of in vivo Pharmacological Activity reported on pages 26-27 of the

applicant's specification (that the 17α-furan-2-yl molecule has demonstrated a surprisingly greater inhibition of lung eosinophilia and reduction of thymus weight as compared to fluticasone propionate) constitutes rebutting evidence of non-obviousness. In light of the manner of the prior art disclosures in issue, and superiority of results, it is respectfully requested that the rejection of claim 4 be withdrawn and the claim be deemed allowable.

b. Claim 7

Claim 7 recites the further limitation that the wherein the solubilising agent recited in claim 4 is a surfactant selected from the group consisting of a α-[4-(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxypoly(oxy-1,2-ethanediyl) polymer (also known as a octylphenoxypolyethoxyethanol) and a 4-(1,1,3,3-Tetramethylbutyl)phenol polymer with formaldehyde and oxirane.

The examiner's assertion that Straub would suggest to one of ordinary skill in the art to select octylphenoxypolyethoxyethanol (a.k.a. Triton), couple it with the 17α-furan-2-yl ester of fluticasone as recited in claim 7, in view of Adjei's laundy list disclosure of a number of unknown classes fluticasone esters having no demonstrated activity, to create a micellular aqueous glucocorticoid solution formulation as described in Sjoquist, is respectfully traversed. First, one would not be directed by the teachings of Adjei to reformulate an undisclosed member of a class of compounds as described in the discussion on claim 4. Further, the Straub reference relates to the manufacture of porous drug particles. The active component of the particles, which is in solid form, allegedly operates by dissolving at a greater rate when contacted in an aqueous media by preparing the drug in a high surface area porous microparticulate structure. In inhaled versions, it is delivered as a dry powder. The microporous structure of the drug particles is formed preferably when the microparticles are contacted by an aqueous media—i.e., in an aqueous system, the drug forms a porous structure which exists in suspension in the aqueous media. (see., Straub, col. 2, lines 15-20). The Straub reference states that: "The matrices may contain hydrophilic excipients such as water soluble polymers or sugars, which can serve as bulking agents or as wetting agents, wetting agents such as surfactants or sugars, and tonicity agents. Upon contact with an aqueous medium, water penetrates through the highly porous matrix to dissolve the water-soluble excipients in the matrix. In the case of

low solubility drugs, a suspension of drug of drug particles in an aqueous medium is left. The total surface area of the resultant low aqueous solubility drug microparticle is increased relative to the unprocessed drug and the dissolution rate is increased." (Straub, col. 8, lines 10-21). Straub continues stating "Wetting agents can be used to facilitate water ingress into the matrix and wetting of the drug particles in order to facilitate dissolution. (Col 9, lines 3-6). Straub relies on the use of the wetting agent, a term including within its scope surfactants, to itself dissolve upon contact with the aqueous media, thus creating a suspension of the drug in the aqueous medium. Straub's increase in dissolution of drug merely refers to the greater dissolution of the porous hydrophobic drugs when compared to drug particles in a non-microporous form. The surfactants thus act as bulking or wetting agents to create suspensions, not to cause the drug to form a solution as claimed. As such, one would not be motivated by the teachings of Straub to select Triton, or polyoxyethylene in order to create a aqueous solution of the compounds as claimed in the instant claim. In light of this distinction, applicants respectfully request that this finding of obviousness be withdrawn, and the claim be found allowable.

c. Claim 10

Claim 10 depends from claim 7, and has been rejected as obvious over Sjoquist, in light of Adjei and Straub. Claim 10 is non-obvious for the reasons identified in the discussion of Claim 7. Claim 10 specifically requires a hydroxy containing organic co-solvating agent or phosphatidyl choline. Applicant have reviewed the Sjoquist and Straub references but have been unable to identify the specific disclosure relied upon by the examiner as teaching a hydroxy containing organic co-solvating agent or phosphatidyl choline.

The examiner points out that Sjoquist discloses the optional use of glucose. Sjoquist does so to act as an isotonicity-adjusting agent however (see, page 7, line 23). As glucose is not acting as a co-solvating agent, as claimed in the present claim, this disclosure appears irrelevant.

In light of the reasons provided in the discussion of claim 7, and in the reasons provided immediately above, applicants request that the examiner withdraw the rejection of claim 10 for the reasons specified. If this request is not granted, the examiner is requested to specifically identify the text from the cited references

disclosing a hydroxy containing organic co-solvating agent or phosphatidyl choline as claimed.

d. Claim 12

Claim 12 depends from claim 10. Applicants respectfully requested the withdraw of the obviousness rejection for the reasons set forth in regard to Claim 10.

In addition to the elements of claim 10, Claim 12 recites that the hydroxy containing organic co-solvating agent is dextrose. Applicant has been unable to find a disclosure in Sjoquist, Adjei or Straub of the use of a co-solvent, or the use of dextrose, or of the use of dextrose as a co-solvating agent, as in the instant claim. As mentioned above, although Sjoquist discloses the optional use of glucose, glucose acts as an isotonicity-adjusting agent (Sjoquist, page 7, line 23), and not a co-solvating agent. As the use of dextrose as a co-solvent has not been disclosed in the art relied upon by the examiner, each and every limitation of the claimed invention is not found in the prior art, and a finding or obviousness cannot be supported as a matter of law. Applicants respectfully request that the examiner withdraw the rejection of claim 12 and allow the claim to pass to issuance. If this request is not granted, the examiner is requested to specifically identify where dextrose is disclosed in the text of these references.

As a matter of record, claim 12 has been amended to remedy a typographical error.

e. Claims 13, 14 and 15.

Claims 13 and 15, as amended, depend from claim 4. Claim 14 is dependent on claim 13. These claims are patentable for the same reasons expressed for the patentablity of claim 4. Allowance of these claims is therefore requested.

2. Claims 6, 8, and 16-18

a. Claim 6

Claim 6 requires that the aqueous carrier have dissolved therein a solubilising agent for assisting the solubilisation of the medicament in the aqueous carrier liquid, wherein the solubilising agent is a surfactant selected from the group consisting of a α-[4-(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxypoly(oxy-1,2-ethanediyl) polymer

(also known as a octylphenoxypolyethoxyethanol) and a 4-(1,1,3,3-Tetramethylbutyl)phenol polymer with formaldehyde and oxirane.

As mention in the discussion of the Straub reference above with regard to Claim 7, Straub relates to the manufacture of porous drug particles. The drug component of the particles is alleged to dissolve at a greater rate when contacted in an aqueous media by preparing the drug in a high surface area porous microparticulate structure. This microporous structure is formed preferably when the microparticles is contacted by the aqueous media—i.e., in an aqueous system, the drug forms a porous structure which exists in suspension in the aqueous media. Straub relies on the use of the "wetting agent" (a term including within its scope surfactants) to itself dissolve upon contact with the aqueous media, to leave the drug matrix in solid form and thus create a suspension of drug in the aqueous media. Straub's increase in dissolution of drug merely refers to the greater dissolution of porous hydrophobic drugs when compared to drug particles in a non-microporous form. The surfactants thus act as bulking or wetting agents, but do not act to cause the drug to form a solution when in an aqueous medium. As such, one would not be motivated by the teachings of Straub to select Triton, or polyoxyethylene in order to create a aqueous solution of the compounds as claimed in the instant claim. Especially as Straub teaches that such water-soluble materials leave these hydrophobic drug materials suspended in the liquid media.

Withdrawal of the rejection of Claim 6 is respectfully requested.

b. Claim 8

Claim 8 specifies that the surfactant of claim 6 is a 4-(1,1,3,3-Tetramethylbutyl)phenol polymer with formaldehyde and oxirane. The examiner rejected this claim over Sjoquist in view of Straub. As mentioned above with claim 6, Straub would not have directed of ordinary skill in the art to make such a combination. Further though, applicant has been unable to identify where in the Straub reference the specified subject matter is disclosed. Absent this showing, all elements of the claim are not disclosed in the prior art, and no showing of obviousness can be established as a matter of law. Allowance of Claim 8 is therefore requested.

c. Claims 16-18

New claims 16-18 are dependent directly or indirectly on claim 6. These claims are allowable for the same reasons set forth above for claim 6.

3. Claims 9, 11, 19-21

a. Claim 9

Claim 9 has been rewritten in independent form, incorporating limitations of cancelled claim 1. Claim 9, as amended, recites:

> A pharmaceutical formulation comprising an aqueous carrier liquid having dissolved therein (a) an ester of fluticasone or a solvate thereof as medicament (b) a solubilising agent for assisting the solubilisation of the medicament in the aqueous carrier liquid, and (c) a hydroxy containing organic co-solvating agent or phosphatidyl choline.

This claim stands rejected as being anticipated by Sjoquist. However, Applicants, having reviewed the Sjoquist reference, have been unable to identify the specific disclosure relied upon by the examiner is establishing this rejection. The examiner mentions Sjoquists use of glucose. However, Sjoquist discloses the optional use of glucose as an isotonicity-adjusting agent (page 7, line 23), and not a co-solvating agent as claimed in the present claim. As such, Applicants request that the examiner withdraw the rejection of claim 9 and allow this claim, as the reference fails to teach each limitation of the claim. Alternatively, the examiner is requested to identify with specificity where in the Sjoquist reference a hydroxy containing organic co-solvating agent or phosphatidyl choline is disclosed, so that applicant's may respond accordingly.

b. Claim 11

Claim 11 depends from claim 9 and recites that the hydroxy containing organic co-solvating agent is dextrose. Claim 11 currently stands rejected as anticipated in view of Sjoquist. As mentioned above in relation to claim 12 above, Sjoquist does not describe the use of a co-solvent, the use of dextrose for any purpose, let alone the use of dextrose as a co-solvating agent. Although Sjoquist discloses the optional use of glucose, glucose acts as an isotonicity-adjusting agent (Sjoquist, page 7, line 23) and not a co-solvating agent as claimed in the present claim. As dextrose

as a co-solvent agent has not been disclosed in the art relied upon by the examiner, each and every limitation of the claimed invention is not found in the cited reference, and a finding of anticipation cannot be supported as a matter of law. Applicants respectfully assert that claim 11 is in a condition for allowance, and requests that the examiner withdraw the rejection of claim 11.

As a matter of record, claim 11 was amended to correct a clear typographical error.

c. Claims 19-21

Added claims 19-21 are dependent directly or indirectly on claim 9, and are patentable for the same reasons.

Conclusion

In light of the cancellation of claims 1, 2, 3 and 5, and the amendments and arguments made herein, Applicant requests that a timely Notice of Allowance be issued in this case. If any matters exist that preclude issuance of a Notice of Allowance, the examiner is requested to contact the applicant's representative at the number indicated below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge any fees or credit any overpayment, particularly including any fees required under 37 CFR Sections 1.16 and/or 1.17, and any necessary extension of time fees, to deposit Account No. 07-1392.

Respectfully submitted,

Dated: 21 July 2003

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